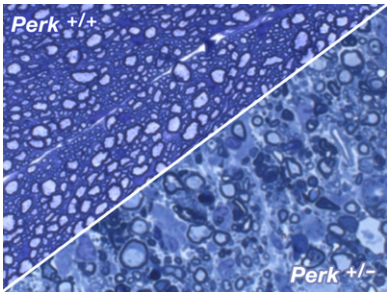
Autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, are complex disorders characterized by an inflammatory response against the body's own tissues. Recent findings reveal new insights into how these diseases are initiated and progress and the factors that contribute to their clinical symptoms. Such work also pinpoints potential new therapeutic targets including the integrated stress response, cadherins, and Wnt signaling.

An IL-1 Wind that Blows No Good

Mast cells of the immune system are on the frontline in the war against bacterial and parasitic invaders. Despite their commendable efforts, when mast cells get trigger-happy—attacking both friend and foe alike—autoimmune disorders or allergy may be the result. The dark tendencies latent in mast cells are further explored by Nigrovic et al. (2007) using a mouse model in which inflammatory arthritis is induced by the presence of autoreactive antibodies. In previous work, animals lacking mast cells were found to be resistant to this type of experimental arthritis. Nigrovic et al. now provide evidence that mast cells are directly activated by immune complexes containing these autoantibodies, resulting in their production of the inflammatory cytokine interleukin-1 (IL-1). Moreover, by simply administering a brief course of IL-1 the authors were able to stimulate arthritis in animals that lacked mast cells. These findings suggest that mast cell IL-1 is needed to marshal leukocytes to affected joints in the initial stages of the inflammatory response yet may be dispensable for the maintenance of arthritis thereafter. Interestingly, in humans, autoantibodies have been observed in serum long before symptoms of rheumatoid arthritis become apparent. If the contribution of mast cells to human rheumatoid arthritis is similar to that described in this mouse model, the compelling question is which factors beyond the presence of autoantibodies dictate the timing of mast cell activation in human disease.
P.A. Nigrovic et al. (2007). Proc. Natl. Acad. Sci. USA ***104****, 2325–2330. Published online February 2, 2007. 10.1073/pnas.0610852103.*

Stress of a Healthy Variety

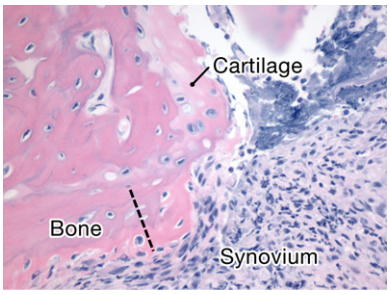


IFN-γ protects against EAE-induced demyelination in *Perk* wild-type mice, but not in mice heterozygous for a null *Perk* allele (toluidine blue stain). Image courtesy of B. Popko.

Multiple sclerosis is an autoimmune disorder in which neuronal axons of the central nervous system are targeted for demyelination. Lin et al. (2007) recently characterized the role of interferon-γ (IFN-γ) in the early stages of experimental autoimmune encephalomyelitis (EAE) in mice, which shares some similarities with human multiple sclerosis. EAE can be triggered when mice are immunized with a peptide derived from the myelin/oligodendrocyte glycoprotein (MOG). Although IFN-γ, a proinflammatory cytokine, is generally thought to promote myelin damage in multiple sclerosis and in EAE, there is also evidence that it may have beneficial effects as well. The work by Lin et al. establishes that the timing of IFN-γ expression is critical. If IFN-γ (expressed from a transgene) is induced in the central nervous system at the time of MOG immunization it decreases the severity of EAE, preventing demyelination and the loss of oligodendrocytes, the cells that myelinate the axons. The authors suggest that the beneficial effect of IFN-γ is linked to the induction of the integrated stress response. This response is an endoplasmic reticulum stress pathway in which the pancreatic endoplasmic reticulum kinase (PERK) phosphorylates the α subunit of eukaryotic translation initiation factor 2 to suppress protein translation. Following the induction of IFN-γ expression, PERK is activated in oligodendrocytes. Moreover, PERK-deficient mice do not respond to the protective effects of early expression of IFN-γ. These findings suggest that protecting cells from the inflammatory response, for example by the timely induction of ER stress, might help to prevent tissue damage in autoimmune diseases.
W. Lin et al. (2007). J. Clin. Invest. ***117****, 448–456.*

Cadherin-11 and Arthritis Are Joined at the Hip

The synovium is a tissue that lines the space surrounding the joints, and it becomes inflamed in rheumatoid arthritis. In the course of the disease, the synovium substantially increases in size due to the infiltration of inflammatory cells and because of enhanced proliferation of cells resident within the synovial lining. In a mouse model of arthritis, Lee et al. (2007) examined the role of cadherin-11, a homophilic adhesion molecule expressed by fibroblast-like cells of the



The arthritic synovium erodes bone and cartilage in the ankle of a wild-type mouse (hematoxylin-eosin stain). Image courtesy of D.M. Lee.

synovial lining. Remarkably, they discovered that mice lacking cadherin-11 are resistant to autoantibody-induced arthritis and do not display the changes in the synovial lining that characterize the disease. Moreover, directly targeting cadherin-11 (using either a cadherin-11-Fc fusion protein or an anti-cadherin-11 monoclonal antibody) reduced the severity of autoantibody-induced arthritis in wild-type mice. These finding indicate that impairing the response of synovial fibroblasts to inflammatory signals might offer a new strategy to combat arthritis. Interestingly, although destruction of cartilage and local bone loss are both observed in this mouse model, the loss of cadherin-11 only alleviated the effect on cartilage, most likely by impairing the invasion of cartilage by synovial cells. Future work may establish other features of synovial cells that could be targeted to protect against bone loss associated with rheumatoid arthritis.

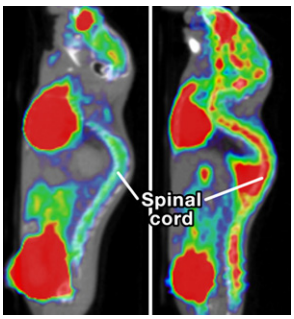
*D.M. Lee et al. (2007). Science **315**, 1006–1010. Published online January 25, 2007. 10.1126/science.1137306.*

Getting the Skinny on Dickkopf-1

Although bone loss is frequently a feature of rheumatoid arthritis, it is not universal among inflammatory joint diseases. For instance, ankylosing spondylitis, a degenerative inflammatory disorder affecting the spine, is characterized by excess bone growth that can eventually lead to fusion of the vertebrae. Diarra et al. (2007) sought to identify signaling pathways in cells involved in bone homeostasis that might determine these opposing responses. They focused their efforts on Dickkopf-1, an inhibitor of Wnt signaling, reasoning that it might counter the bone-promoting effects of Wnt signaling that have been reported during development. They observed that Dickkopf-1 expression is enhanced in the synovium in human patients with rheumatoid arthritis and in multiple mouse models of the disease. Interestingly, the expression of Dickkopf-1 does not follow this trend in individuals with ankylosing spondylitis. In mouse models of rheumatoid arthritis, an anti-Dickkopf-1 antibody halts bone loss in the joint and promotes the growth of osteophytes (bone spurs), a frequent clinical feature of ankylosing spondylitis. Diarra et al. also provide evidence that Dickkopf-1 blockade enhances Wnt signaling in synovial fibroblasts, as evidenced by an increase in nuclear β-catenin, suggesting that signals from the synovial fibroblasts direct bone production and resorption. Thus, Wnt signaling sits at a key tipping point in inflammatory joint disease, such that increased Wnt signaling in rheumatoid arthritis or decreased Wnt signaling in ankylosing spondylitis might alleviate some of the debilitating effects of these diseases.

*D. Diarra et al. (2007). Nat. Med. **13**, 156–163. Published online January 21, 2007. 10.1038/nm1538.*

An Autoimmune Disease Caught in the Act



PET/CT imaging shows that glycolysis in the spinal cord is higher in mice with EAE (right) than in unimmunized controls (left). Image courtesy of C.G. Radu.

An increase in glycolysis is observed in many immune cells after they have become activated. According to Radu et al. (2007), it might one day be possible using this metabolic signature to monitor the progression and treatment of autoimmune disorders using variations on existing imaging technology. Indeed, tumor cells, which display an increased rate of glycolysis, are routinely imaged using positron emission tomography (PET) with the glucose analog 2-[^{18}F]Fluoro-2-deoxy-D-glucose ([^{18}F]-FDG) in combination with computed tomography (CT), which provides detailed anatomical information. Radu et al. took a similar approach combining [^{18}F]-FDG PET and high-resolution CT imaging to study immune cell infiltration in experimental autoimmune encephalomyelitis (EAE) in mice. They observed that mice with EAE display enhanced glycolysis in the spinal cord, likely due to the infiltration of activated T cells that target myelin, and that this increase in activity correlated with the onset of symptoms. Likewise, when EAE mice were treated with dexamethasone, previously shown to suppress T cell activity and prevent the development of EAE, a decrease in glycolysis was observed. Although it is not yet clear whether this kind of imaging will prove useful in predicting the onset of symptoms in autoimmune diseases, these efforts suggest that metabolic imaging might be used to provide an early indicator of efficacy for future treatments that target hyperactive immune cells.

*C.G. Radu et al. (2007). Proc. Natl. Acad. Sci. USA **104**, 1937–1942. Published online January 29, 2007. 10.1073/pnas.0610544104.*

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